

degenerated oligonucleotides and comprising up to four amino acid substitutions, a CDRL2 derived from SEQ ID NO: 33 by oligonucleotide-directed mutagenesis using degenerated oligonucleotides and comprising up to four amino acid substitutions, a CDRL3 derived from SEQ ID NO: 34 by oligonucleotide-directed mutagenesis using degenerated oligonucleotides and comprising up to four amino acid substitutions,

c) the second binding part comprises a light chain variable region, comprising as CDRL1, CDRL2 and CDRL3 a CDRL1 of SEQ ID NO: 18, a CDRL2 of SEQ ID NO: 19 and a CDRL3 of SEQ ID NO: 20.

Such bispecific antibodies are, but not limited, bispecific anti CEAxCD3 antibodies AB13L3-1, AB14L3-1, AB15L3-1, AB17L3-1, AB20L3-1, AB54L3-1, AB60L3-1, AB66L3-1, AB71L3-1, AB72L3-1, and AB73L3-1.

In one aspect, the present disclosure refers to a bispecific antibody comprising a first binding part, specifically binding to human CEACAM5 and a second binding part, specifically binding to human CD3ε, characterized in that:

a) the first binding part comprises a heavy chain variable region VH, which comprises as CDRH1, CDRH2, and CDRH3 a CDRH1 of SEQ ID NO: 2, a CDRH2 of SEQ ID NO: 3 and a CDRH3 of SEQ ID NO: 4,

b1) a CDRL1 of SEQ ID NO: 90, CDRL2 of SEQ ID NO: 91, and CDRL3 of SEQ ID NO: 92,

b2) a CDRL1 of SEQ ID NO: 96, CDRL2 of SEQ ID NO: 97, and CDRL3 of SEQ ID NO: 98,

b3) a CDRL1 of SEQ ID NO: 99, CDRL2 of SEQ ID NO: 100, and CDRL3 of SEQ ID NO: 101,

b4) a CDRL1 of SEQ ID NO: 102, CDRL2 of SEQ ID NO: 103, and CDRL3 of SEQ ID NO: 104,

b5) a CDRL1 of SEQ ID NO: 105, CDRL2 of SEQ ID NO: 106, and CDRL3 of SEQ ID NO: 107,
b6) a CDRL1 of SEQ ID NO: 108, CDRL2 of SEQ ID NO: 109, and CDRL3 of SEQ ID NO: 110,
and

b7) a CDRL1 of SEQ ID NO: 111, CDRL2 of SEQ ID NO: 112, and CDRL3 of SEQ ID NO: 113,
and

c) the second binding part comprises a heavy chain variable region VH comprising a CDRH1 of
SEQ ID NO: 2, CDRH2 of SEQ ID NO: 3 and CDRH3 of SEQ ID NO: 4 and a light chain variable
region VL comprising a CDRL1 of SEQ ID NO: 18, CDRL2 of SEQ ID NO: 19, and CDRL3 of
SEQ ID NO: 20.

In one example the bispecific antibody is characterized in comprising a first binding part,
specifically binding to human CEACAM5 and a second binding part, specifically binding to human
CD3ε, characterized in that:

a) the first binding part comprises a heavy chain variable region VH, which comprises as CDRH1,
CDRH2, and CDRH3 a CDRH1 of SEQ ID NO: 2, a CDRH2 of SEQ ID NO: 3 and a CDRH3 of
SEQ ID NO: 4,

b) the first binding part comprises as light chain variable region a light chain variable region
comprising a CDRL set selected from the group consisting of

b1) a CDRL1 of SEQ ID NO: 90, CDRL2 of SEQ ID NO: 91, and CDRL3 of SEQ ID NO: 92,

b2) a CDRL1 of SEQ ID NO: 96, CDRL2 of SEQ ID NO: 97, and CDRL3 of SEQ ID NO: 98,

b3) a CDRL1 of SEQ ID NO: 99, CDRL2 of SEQ ID NO: 100, and CDRL3 of SEQ ID NO: 101,

b4) a CDRL1 of SEQ ID NO: 102, CDRL2 of SEQ ID NO: 103, and CDRL3 of SEQ ID NO: 104,

b5) a CDRL1 of SEQ ID NO: 105, CDRL2 of SEQ ID NO: 106, and CDRL3 of SEQ ID NO: 107,
and

b6) a CDRL1 of SEQ ID NO: 111, CDRL2 of SEQ ID NO: 112, and CDRL3 of SEQ ID NO: 113,
and

c) the second binding part comprises a heavy chain variable region VH comprising a CDRH1 of
SEQ ID NO: 2, CDRH2 of SEQ ID NO: 3 and CDRH3 of SEQ ID NO: 4 and a light chain variable
region VL comprising a CDRL1 of SEQ ID NO: 18, CDRL2 of SEQ ID NO: 19, and CDRL3 of
SEQ ID NO: 20.

In one example, the disclosure refers to a bispecific antibody, characterized in comprising in the first binding part

a) a common heavy chain selected from the group consisting of

a1) the heavy chain of SEQ ID NO: 43,

5 a2) the heavy chain of SEQ ID NO: 44, or

a3) the heavy chain of SEQ ID NO: 45, and

b) a light chain selected from the group consisting of

b1) the light chain of SEQ ID NO: 40

b2) the light chain of SEQ ID NO: 125,

10 b3) the light chain of SEQ ID NO: 126,

b4) the light chain of SEQ ID NO: 127,

b5) the light chain of SEQ ID NO: 128,

b6) the light chain of SEQ ID NO: 129,

b7) the light chain of SEQ ID NO: 130,

15 b8) the light chain of SEQ ID NO: 131

b9) the light chain of SEQ ID NO: 132,

b10) the light chain of SEQ ID NO: 133

b11) the light chain of SEQ ID NO: 134, or

b12) the light chain of SEQ ID NO: 135, and

20 c) in the second binding part a light chain of SEQ ID NO: 28.

In one example a bispecific antibody according to the disclosure (AB17L3-1/N) comprises a common heavy chain of SEQ ID NO: 45 (/N) and in the second binding part as light chain a light

chain of SEQ ID NO: 28 (1A4 LC respectively L3-1) and in the first binding part as light chain a

25 light chain of SEQ ID NO: 128 (AB17). In one example a bispecific antibody according to the

disclosure (AB71L3-1/N) comprises a common heavy chain of SEQ ID NO: 45 (/N) and in the

second binding part as light chain a light chain of SEQ ID NO: 28 (L3-1) and in the first binding

part as light chain a light chain of SEQ ID NO: 133 (AB71). In one example a bispecific antibody

according to the disclosure (AB73L3-1/N) comprises a common heavy chain of SEQ ID NO: 45

30 (/N) and in the second binding part as light chain a light chain of SEQ ID NO: 28 (L3-1) and in the

first binding part as light chain a light chain of SEQ ID NO: 135 (AB73).

CLAIMS

1. A bispecific antibody comprising a first binding part, specifically binding to human CEACAM5, and a second binding part, specifically binding to human CD3ε, wherein:

a) the first binding part comprises a heavy chain variable region (VH), which comprises a CDRH1 of SEQ ID NO: 2, a CDRH2 of SEQ ID NO: 3 and a CDRH3 of SEQ ID NO: 4,

b) the first binding part comprises a light chain variable region (VL) comprising a CDRL set selected from the group consisting of

b1) a CDRL1 of SEQ ID NO: 90, CDRL2 of SEQ ID NO: 91, and CDRL3 of SEQ ID NO: 92,

b2) a CDRL1 of SEQ ID NO: 96, CDRL2 of SEQ ID NO: 97, and CDRL3 of SEQ ID NO: 98,

b3) a CDRL1 of SEQ ID NO: 99, CDRL2 of SEQ ID NO: 100, and CDRL3 of SEQ ID NO: 101,

b4) a CDRL1 of SEQ ID NO: 102, CDRL2 of SEQ ID NO: 103, and CDRL3 of SEQ ID NO: 104,

b5) a CDRL1 of SEQ ID NO: 105, CDRL2 of SEQ ID NO: 106, and CDRL3 of SEQ ID NO: 107,

b6) a CDRL1 of SEQ ID NO: 108, CDRL2 of SEQ ID NO: 109, and CDRL3 of SEQ ID NO: 110, and

b7) a CDRL1 of SEQ ID NO: 111, CDRL2 of SEQ ID NO: 112, and CDRL3 of SEQ ID NO: 113,

c) the second binding part comprises a VH comprising a CDRH1 of SEQ ID NO: 2, CDRH2 of SEQ ID NO: 3 and CDRH3 of SEQ ID NO: 4, and

d) the second binding part comprises a VL comprising a CDRL1 of SEQ ID NO: 18, CDRL2 of SEQ ID NO: 19, and CDRL3 of SEQ ID NO: 20.

2. The bispecific antibody according to claim 1, comprising

a) in the first binding part a heavy chain variable region VH of SEQ ID NO: 1,

b) in the first binding part a light chain variable region VL selected from the group consisting of

b1) a light chain variable region VL of SEQ ID NO: 117,

b2) a light chain variable region VL of SEQ ID NO: 119,

b3) a light chain variable region VL of SEQ ID NO: 120,
b4) a light chain variable region VL of SEQ ID NO: 121,
b5) a light chain variable region VL of SEQ ID NO: 122,
b6) a light chain variable region VL of SEQ ID NO: 123, and
5 b7) a light chain variable region VL of SEQ ID NO: 124, and
c) in the second binding part a heavy chain variable region VH of SEQ ID NO: 1 and a light chain variable region VL of SEQ ID NO: 17.

3. The bispecific antibody according to claim 2, comprising

10 a) in the first binding part a heavy chain variable region VH of SEQ ID NO: 1,
b) in the first binding part a light chain variable region VL selected from the group consisting of
b1) a light chain variable region VL of SEQ ID NO: 117,
b2) a light chain variable region VL of SEQ ID NO: 122, and
15 b3) a light chain variable region VL of SEQ ID NO: 124, and
c) in the second binding part a heavy chain variable region VH of SEQ ID NO: 1 and a light chain variable region VL of SEQ ID NO: 17.

4. The bispecific antibody according to claim 1, comprising

20 a) in the first binding part a heavy chain variable region VH of SEQ ID NO: 1,
b) in the first binding part a light chain selected from the group consisting of
b1) the light chain of SEQ ID NO: 128,
b2) the light chain of SEQ ID NO: 130,
b3) the light chain of SEQ ID NO: 131
25 b4) the light chain of SEQ ID NO: 132,
b5) the light chain of SEQ ID NO: 133,
b6) the light chain of SEQ ID NO: 134, and
b7) the light chain of SEQ ID NO: 135, and
c) in the second binding part a heavy chain variable region VH of SEQ ID NO: 1 and a light
30 chain of SEQ ID NO: 28.

5. The bispecific antibody according to any one of claims 1 to 4, characterized in comprising a common heavy chain selected from the group consisting of
- a) the heavy chain of SEQ ID NO: 43,
 - b) the heavy chain of SEQ ID NO: 44, and
 - 5 c) the heavy chain of SEQ ID NO: 45.
6. The bispecific antibody according to claim 1 comprising a common heavy chain of SEQ ID NO: 45 and in the second binding part a light chain of SEQ ID NO: 28 and in the first binding part a light chain of SEQ ID NO: 128.
- 10 7. The bispecific antibody according to claim 1 comprising a common heavy chain of SEQ ID NO: 45 and in the second binding part a light chain of SEQ ID NO: 28 and in the first binding part a light chain of SEQ ID NO: 133.
- 15 8. The bispecific antibody according to claim 1 comprising a common heavy chain of SEQ ID NO: 45 and in the second binding part a light chain of SEQ ID NO: 28 and in the first binding part a light chain of SEQ ID NO: 135.
- 20 9. The bispecific antibody according to any one of claims 1 to 8, wherein the bispecific antibody comprises an IgG Fc domain and each subunit of the Fc domain comprises the amino acid substitutions L234A, L235A and P329A (Kabat EU index numbering).
10. Use of the bispecific antibody according to any one of claims 1 to 9 in the manufacture of a medicament for treating colorectal cancer, non-small cell lung cancer (NSCLC), gastric cancer, pancreatic cancer and/or breast cancer that expresses CEA.
- 25 11. Use of the bispecific antibody according to any one of claims 1 to 9 in the manufacture of a medicament for treating carcinomas that express CEA.
- 30 12. The bispecific antibody according to any one of claims 1 to 9 for use in therapy.

13. Use of the bispecific antibody according to any one of claims 1 to 9 in the manufacture of a medicament for treating colorectal carcinoma, esophageal cancer, pancreatic adenocarcinoma, gastric cancer, non-small cell lung cancer, breast cancer, head and neck carcinoma, uterine and bladder cancers that express CEA.

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14. Use of the bispecific antibody according to any one of claims 1 to 9 in the manufacture of a medicament for use as a monotherapy for the treatment of CEA expressing solid tumors.

10 15. Use of the bispecific antibody according to any one of claims 1 to 9 in the manufacture of a first medicament and use of pembrolizumab, nivolumab, pidilizumab, or lambrolizumab in the manufacture of a second medicament, wherein the first and the second medicament are for use in combination therapy to treat cancer that expresses CEA, wherein the first and the second medicaments are to be administered simultaneously, separately, or sequentially.

15 16. The bispecific antibody of claim 12 or the use according to any one of claims 10 to 11 and 13 to 15, wherein the medicament is to be administered to a patient in doses ranging from 0.1 to 100 mg/kg of body weight per day or per week in single or divided doses, or by continuous infusion.

20 17. The use according to claim 15, wherein pembrolizumab, nivolumab, pidilizumab, or lambrolizumab is to be administered to a patient in doses ranging from 0.1 to 100 mg/kg of body weight per day or per week in single or divided doses, or by continuous infusion.

25 18. A pharmaceutical composition comprising a bispecific antibody according to any one of claims 1 to 9 and a pharmaceutically acceptable carrier.

19. Use of the bispecific antibody of any one of claims 1 to 9, or the pharmaceutical composition of claim 18, in the manufacture of a medicament for treating cancer that expresses CEA in a subject in need thereof.

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20. An isolated polynucleotide that encodes the antibody of any one of claims 1 to 9.

21. A vector comprising the isolated polynucleotide of claim 20.
22. A cell comprising the isolated polynucleotide of claim 20 or the vector of claim 21.
- 5 23. The cell of claim 22, which is selected from the group consisting of Streptomyces, yeast, CHO, YB/20, NS0, PER-C6, HEK-293T, NIH-3T3, HeLa, BHK, Hep G2, SP2/0, R1.1, B-W, L-M, COS 1, COS 7, BSC1, BSC40, BMT10 cell, plant cell, insect cell, and human cell in tissue culture.
- 10 24. A method of making a bispecific antibody, comprising expressing the bispecific antibody in the cell of claim claim 22 or 23.
25. A method of making a bispecific antibody, comprising culturing the cell of claim 22 or 23 and isolating the antibody expressed therein.